REMARKS:

Claims 25-28, 35, 36, 38, and 41-52 are currently pending in this application. With this response, Applicants amend claims 35 and 36, and add new claims 53-60. Applicants also cancel claims 27, 28, 38, 43, 44, and 49-52, expressly reserving the right to pursue the subject matter of the canceled claims in a subsequent application. After entry of this Amendment claims 25, 26, 35, 36, 41, 42, 45-48, and 53-60 will be pending.

New claims 53-60 are added to specify particular neuronal cell embodiments of the invention. Support for the new claims can be found in the specification, for example, at page 17, lines 16-20 (developing neuronal cell), page 18, lines 3-12 (central, peripheral, and neuronal cells capable of dividing), and page 19, lines 23-32 (neural, neuronal stem cells).

Amendments to the Specification

With this response, Applicants amend the specification to correct a minor typographical error in the specification as filed. SEQ ID NO:1 is a nucleotide sequence encoding a bovine BMP-11 polypeptide while SEQ ID NO:11 is an amino acid sequence encoding a human BMP-11 polypeptide. The amended portion of the specification refers to human BMP-11, and thus reference to SEQ ID NO:1 is a clear typographical error.

Obviousness-type Double Patenting Rejection

The Examiner maintains a rejection of the pending claims under the doctrine of obviousness-type double patenting, citing of U.S. Patent No. 6,340,668, and, "if

necessary," U.S. Patent No. 5,700,911. While Applicants do not acquiesce in the double patenting rejection, Applicants submit a terminal disclaimer with this amendment.[1] This terminal disclaimer is effective with respect to any terminal part of any patent granted on the present application that would extend beyond the full term of U.S. Patent No. 6,340,668. Applicants note that the term of U.S. Patent No. 6,340,688 expires before the term of U.S. Patent No. 5,700,911. Applicants therefore request entry of the terminal disclaimer and withdrawal of the double patenting rejection.

Applicants note that the entry of the terminal disclaimer removes the only pending ground for rejection of claims 35, 36, 41, 42, and 45-48. Applicants thus believe that these claims are now in condition for allowance.

Maintained Rejections Under 35 U.S.C. § 112

The Examiner rejects claims 25-28, 38, 43, 44, and 49-52 under 35 U.S.C. § 112, first paragraph as allegedly non-enabled.

The Examiner first alleges that the claims directed to inducing neurite formation are not enabled for inducing neurite formation from any neuronal cell, stating that the working examples are limited to neurite formation in PC12 cells. Without acquiescing in this ground for rejection, Applicants cancel claims 27, 28, 38, 43, 44, and 49-52 with this response. Applicants believe that after amendment this rejection is moot.

The Examiner also objects to the scope of the hybridization limitation of claims 25 and 26. The Examiner notes that the specification is enabling for a method of

[1] In accordance with the Manual of Patent Examining Procedure, the filing of a Terminal Disclaimer "is not an admission of the propriety of the rejection." MPEP § 804.02.II.

promoting neuronal cell survival with a polypeptide comprising amino acids 7-108 of SEQ ID NO:11 or amino acids 1-109 of SEQ ID NO:11. However, he alleges that the specification does not reasonably provide enablement for a method of promoting neuronal cell survival with a polypeptide encoded by a nucleic acid molecule that hybridizes under stringent conditions with the complement of (i) nucleotides 778 to 1083 of SEQ ID NO:10, or (ii) a nucleotide sequence that encodes the same amino acid sequence as nucleotides 778 to 1083 of SEQ ID NO:10.

The Examiner states that the Applicants have not shown that hybridization is a repeatable, predicable process of producing variant BMP-11 proteins because Applicants have only obtained BMP-11 proteins that are identical in the carboxyl-terminal, mature portion of the molecule. The Examiner posits that because working examples of neuronal cell survival with a variant form of BMP-11 are not provided, a substantial inventive contribution on the part of a practitioner would be needed to practice the instant invention, "which would involve the determination of those amino acid residues in the amino acid sequence of SEQ ID NO:11 which are required for the structural and functional integrity of the protein."

In response, Applicants first note that while the specification identifies and describes isolation and purification of carboxyl-terminal mature portions of bovine and human BMP-11 protein that are identical at the amino acid level, the application also provides nucleic acid sequences that encode the mature portions of bovine and human BMP-11 proteins which are not identical. A Pearson sequence alignment of the 327 nucleotides of SEQ ID NO:1 and SEQ ID NO:10 that encode mature bovine and mature human BMP-11 demonstrates that the two sequences are approximately 92.7%

identical (aligning nucleotides 375 to 701 of bovine SEQ ID NO:1 with nucleotides 760 to 1086 of human SEQ ID NO:10). Alignments of the two sequences are attached to this response for consideration by the Examiner (Attachment A).

Applicants note that the claims recite hybridizing language that necessarily defines a genus of nucleic acid molecules. As the Examiner recognizes at page 6 of the pending Office Action, this hybridization limitation is a structural limitation of the genus of variant BMP-11 nucleotide sequences, and thus a structural limitation of the polypeptides that are encoded by the BMP-11 nucleotide sequences. The Applicants note that the specification provides variant BMP-11 nucleotide sequences in SEQ ID NOs:1 and 10, as illustrated above. Because multiple nucleic acid sequences are reduced to practice in the specification, the application provides a repeatable, predictable process of producing variant BMP-11 polypeptides. While the Applicants recognize the Examiner's concern that not all nucleic acids that hybridize to nucleotides 778 to 1083 of SEQ ID NO:10 under the recited conditions will necessarily encode a polypeptide that promotes neuronal cell survival, the predictability of this one step cannot be dispositive in determining enablement.

The Applicants do not agree that a skilled practitioner would be required to determine which amino acid residues in the amino acid sequence of SEQ ID NO:11 are required for the structural and functional integrity of the mature portion of the BMP-11 protein to practice the full scope of the invention without undue experimentation. Moreover, the Examiner has failed to establish why such information would be needed to enable the claimed methods. Applicants posit that such information would be readily

available to a person of ordinary skill in the art reading the specification when it was originally filed, based on that person's level of skill and knowledge of the art.

The well-known shared structural characteristics of TGF-β superfamily members, as well as the specification's detailed discussion of how BMP-11 relates to known TGF-β family members, would allow one skilled in the art to readily compare the BMP-11 amino acid sequences provided in this application to known alignments of TGF-β family proteins. Such an alignment and its interpretation would be routine, and well within the skills of a person of ordinary skill in the art. Notably, by the time BMP-11 was isolated and described in this application, ten other highly homologous proteins -- both structurally and functionally -- were known and characterized. Although BMPs are heterogeneous with regard to their biological effects, they were well known to share common structural features essential for the function of each BMP protein.

As analyzed under the factors of *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), the hybridizing and expression experiments require a low quantity of experimentation, because they are likely to succeed. A person of ordinary skill in the art could easily repeat the experiments laid out in the specification to identify additional variant BMP-11 nucleotide sequences from any number of DNA libraries (e.g., libraries made from other species such as chicken or libraries made from disease tissue) with a single step. The application therefore provides a repeatable, predictable, well-known process for generating nucleic acids that share common structural features, and that encode polypeptides that share common structural features. As noted previously, see, e.g., Amendment filed September 19, 2005 at pages 14-15, the application provides functional assays to test the polypeptides encoded by the nucleic acid sequences.

Thus, once the variant sequences are obtained by hybridization and expressed, the quantity of experimentation needed to test whether the encoded proteins promote neuronal cell survival would also be routine.

The instant application provides an eleventh member of the BMP family of proteins and the discovery that this BMP family member promotes the survival of neuronal cells. Thus, this application developed on a well known and sophisticated body of knowledge in this field. Further, the level of the skilled practitioner in the art of molecular biology is high, such as a Ph.D. scientist with substantial research experience.

The application also provides a great deal of direction and guidance, both relating to hybridization and cloning procedures and to the functional assays which assess whether an encoded polypeptide promotes neuronal cell survival. In relation to the presence or absence of working examples, the specification provides hybridization data, hybridization experiments, and it discloses nucleic acid variants. It also shows that a mature BMP-11 polypeptide promotes neuronal cell survival in a well-known assay for cell viability, an assay that measures the metabolic activity of living cells.

The instant claims require that hybridization reactions be carried out under stringent conditions, specifically including washing at 65°C in 0.1x SSC buffer. One skilled in the art can easily calculate the predicted range of homology for sequences that would hybridize to a particular nucleotide sequence (probe sequence) based on knowing the salt concentration, the length of the probe sequence, and the percent GC content of the probe sequence. See, e.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, pp. 387-389 (1982), as cited by Applicants at page 13, lines 31-33

(enclosed as Attachment B). As a matter of routine, a person of ordinary skill could determine the expected range of homology for sequences that would hybridize to the complement of nucleotides 778 to 1083 of SEQ ID NO:10. Calculated as provided in Maniatis, given the stringent hybridization conditions of 0.1x SSC (wherein [Na+] = 0.0165 M) and 65°C defined in the claims and the GC content and length of the sequence, the skilled practitioner could then estimate the number of mismatches tolerated as requiring approximately 92% identity.

Thus the claims are not overly broad, and claims 25 and 26 provide a finite set of variant BMP-11 nucleotide sequences. For these reasons and for the reasons argued at pages 11-16 of the Amendment filed September 19, 2005 in this case, Applicants respectfully ask the Examiner to withdraw the enablement rejection of claims 25 and 26.

New Rejections Under 35 U.S.C. § 112

The Examiner rejects claims 38, 43, 44, and 49-52 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement based on the phrase "neuronal progenitor cell." The Examiner also rejects these claims under 35 U.S.C. § 112, second paragraph based on the same phrase. Without acquiescing in these rejections, Applicants cancel these claims. The rejections are thus moot.

Conclusion

In view of the foregoing amendments and remarks, Applicants believe that the claims now comply with all requirements on 35 U.S.C. § 112, and the application is in condition for allowance.

Applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: June 12, 2006

By: Mary K. Ferguson
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